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DOI:

[10.1016/j.brainresbull.2018.04.004](https://doi.org/10.1016/j.brainresbull.2018.04.004)

*Document Version*

Peer reviewed version

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*Citation for published version (APA):*

Giese, K. P., & Kida, S. (2018). New mechanistic insights into memory processes. *Brain Research Bulletin*.  
<https://doi.org/10.1016/j.brainresbull.2018.04.004>

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## Accepted Manuscript

Title: New mechanistic insights into memory processes

Author: K.P. Giese

PII: S0361-9230(18)30259-4

DOI: <https://doi.org/10.1016/j.brainresbull.2018.04.004>

Reference: BRB 9410

To appear in: *Brain Research Bulletin*

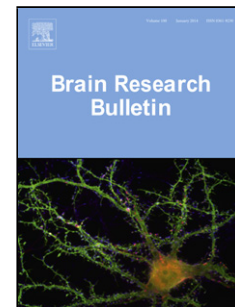
Author: S. Kida

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To appear in: *Brain Research Bulletin*



Please cite this article as: S.Kida, New mechanistic insights into memory processes, Brain Research Bulletin <https://doi.org/10.1016/j.brainresbull.2018.04.004>

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## New mechanistic insights into memory processes

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One of the major goals of neuroscience is to develop a mechanistic understanding of learning and memory processes. Despite decades of intense research, we are still a long way from sufficiently understanding how the brain acquires, stores, retrieves and modifies information and how such processes are affected in diseases. However, the use of novel techniques, including molecular and optogenetic approaches, has significantly advanced the mechanistic understanding of memory processes and their dysfunction in diseases. This *Special Issue* focuses on recently discovered memory mechanisms that function at the molecular, cellular and systems level, which have not yet been covered well in the literature.

Epigenetic regulation is thought to underlie (long-term) memory formation. Shusaku Uchida and Gleb Shumyatsky review not only current knowledge about the role of histone acetylation and DNA methylation in memory formation, they also include a discussion of memory enhancement by CRCTC1-CREB signaling and resulting regulation of Fgf1 transcription (Uchida and Shumayatsky, 2018). At the cellular level, recent findings are emerging that not only excitatory neurons, but also inhibitory interneurons, have an important role for memory formation. Elizabeth Lucas and Roger Clem summarize recent findings that indicate that GABAergic interneurons are critically involved in memory formation (Lucas and

Clem, 2018). Using the example of auditory fear conditioning, they summarize the current knowledge regarding the role of these interneurons in microcircuits in different brain regions, such as auditory cortex, medial prefrontal cortex and amygdalar nuclei. Additionally, Julien Artinian and Jean-Claude Lacaille review the emerging role of somatostatin-positive interneurons in the regulation of long-term potentiation and hippocampus-dependent memory formation (Artinian and Lacaille, 2018). They also discuss the memory-related function of these interneurons in other brain regions, such as cortex. Toshiyuki Tanimizu et al. present a novel immediate-early gene expression analysis to identify the brain networks underlying memory formation, using the object recognition task (Tanimizu et al., 2018). They report that not only hippocampal subregions, but also the medial prefrontal cortex, are activated during memory formation. Adi Doron and Inbal Goshen discuss how memories are stored at a systems level, using novel techniques to investigate the anatomical basis of long-lasting, remote memory (Doron and Goshen, 2018). They also summarize the evidence for and against a long-lasting role of the hippocampus in contextual fear memory storage.

Next, this *Special Issue* addresses the question of how memories are stored, and how they can be modified during retrieval. Patrick Davis and Leon Reijmers discuss a novel principle for memory storage, using as an example of how the basolateral amygdala can function as a storage site for fear memories (Davis and Reijmers, 2018). They propose that oscillatory activity may be a mechanism to support storage and retrieval of fear memory over long time. Lim et al. present novel findings on the role of  $\beta$ -adrenergic signaling in retrieval-induced memory reconsolidation (Lim et al., 2018). They show that, unexpectedly,  $\beta$ -adrenergic signaling is required for memory destabilization and not restabilization. They propose that  $\beta$ -adrenergic signaling regulates neuronal excitability after retrieval. Further, Matthew Rich and Mary Torregossa review the role of extinction and reconsolidation for treating drug-related memories, and they point to molecular mechanisms that ideally affect one,

not both, of these processes (Rich and Torregossa, 2018). Blocking CaMKII activity may be promising for treating drug-related memories, as it appears to enhance extinction and blocks reconsolidation.

Finally, Alzheimer's disease is the most prominent memory disease. Synaptic dysfunction is thought to cause memory impairment in Alzheimer's disease, but what underlies this dysfunction is not well known. Masuo Ohno discusses evidence that abnormal regulation of protein synthesis via PERK kinase impairs synaptic plasticity and memory formation in Alzheimer's disease (Ohno, 2018).

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